



Computer Aided Ligand-Based and Receptor-Based
Drug Design Utilizing Molecular Shape
Inventor(s): Zauhar
Serial No. (if known): 10/635,280
Docket No. 30/1183US

Sheet 1 of 29

REPLACEMENT SHEET

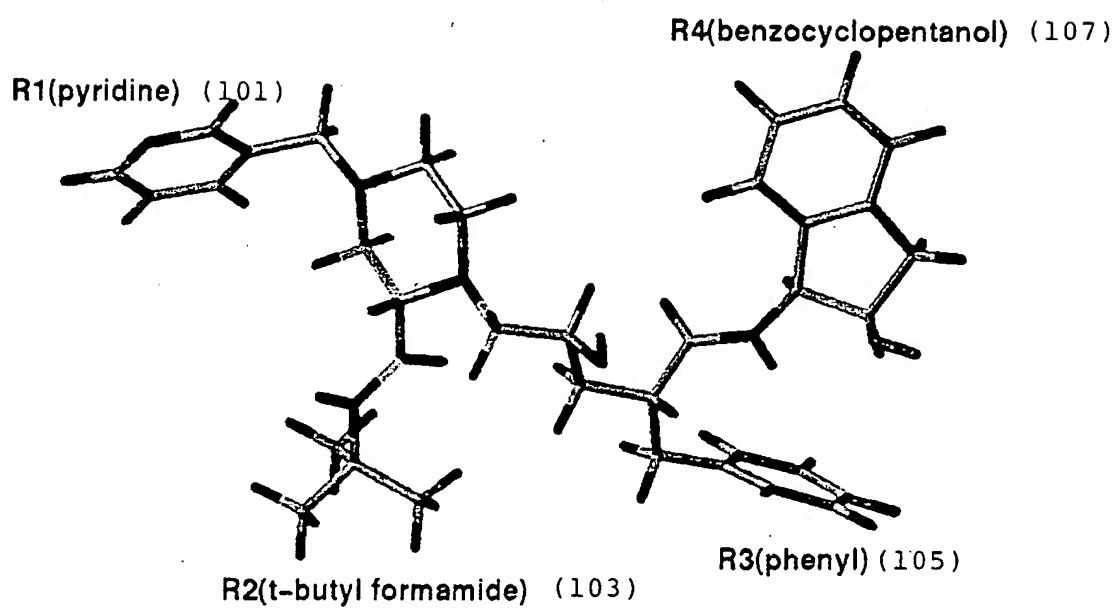


FIG. 1

BEST AVAILABLE COPY

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REPLACEMENT SHEET

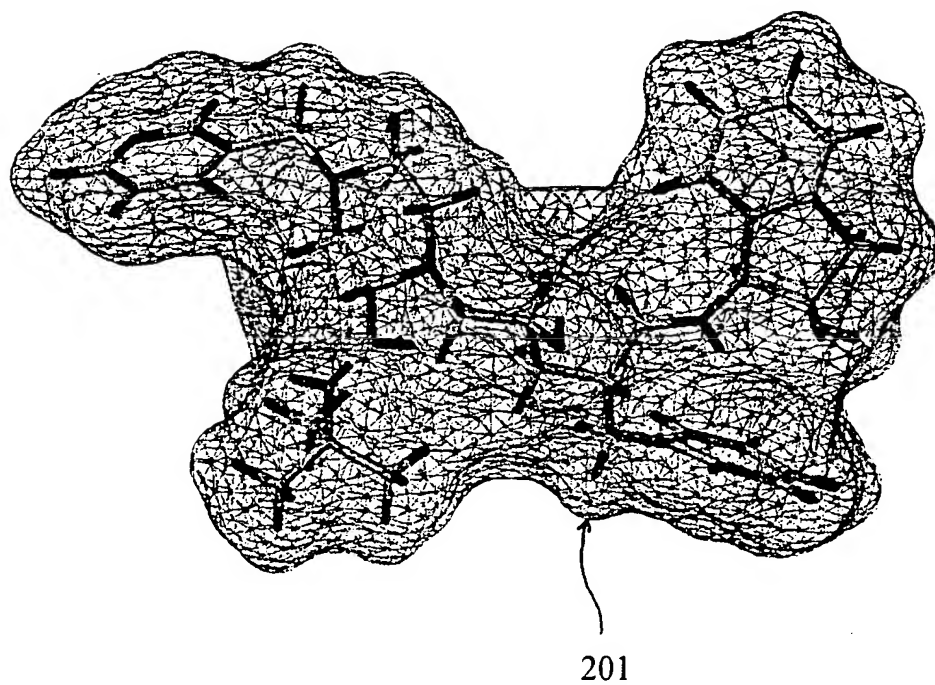


FIG. 2

REPLACEMENT SHEET

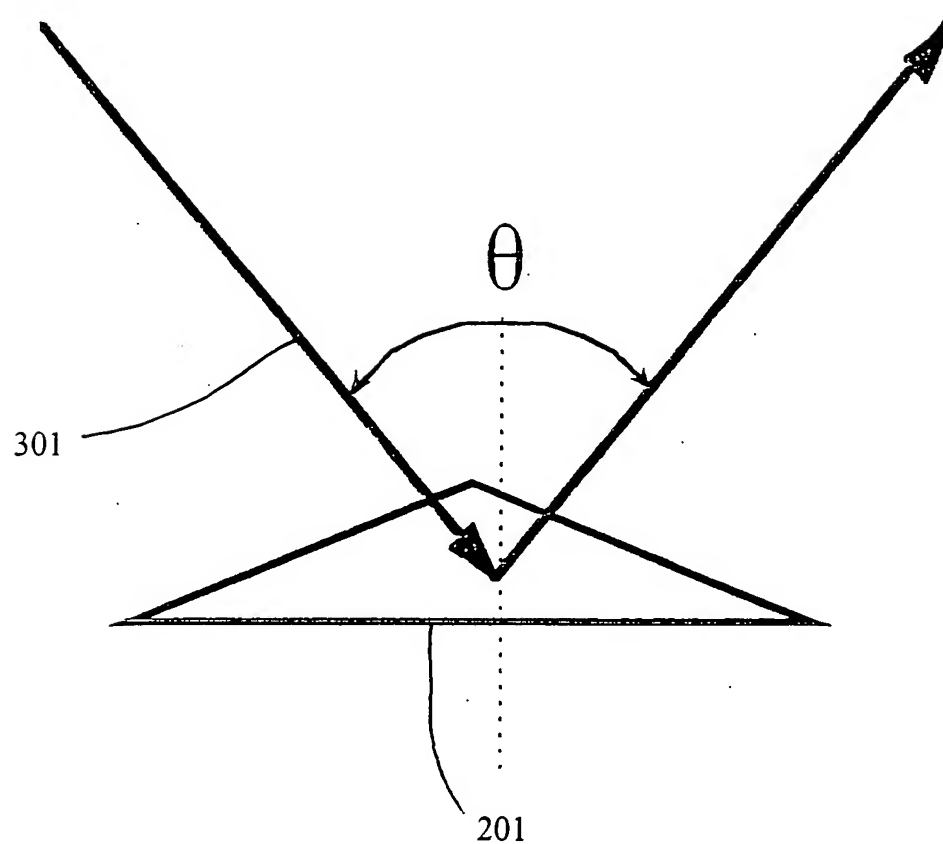


FIG. 3

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REPLACEMENT SHEET

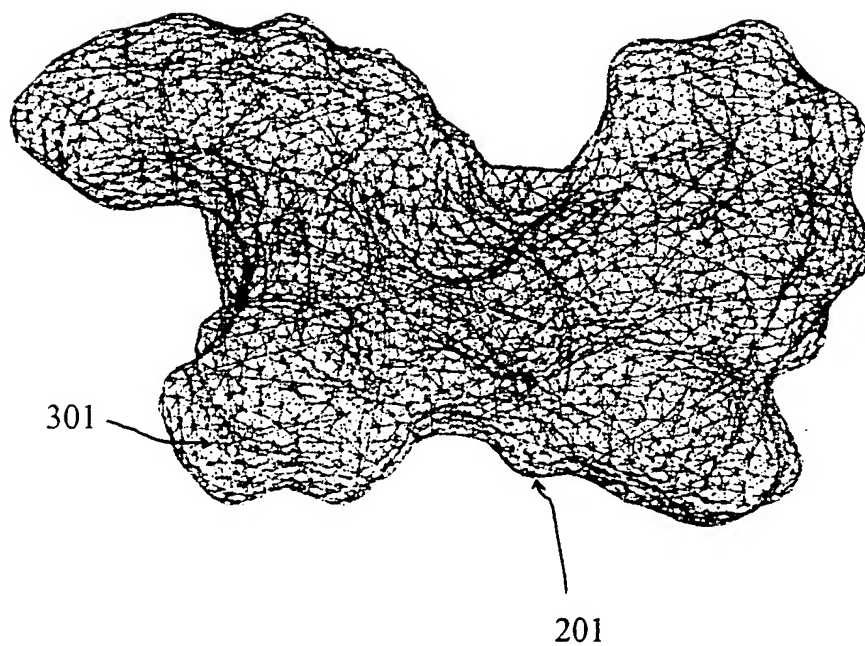


FIG. 4A

REPLACEMENT SHEET

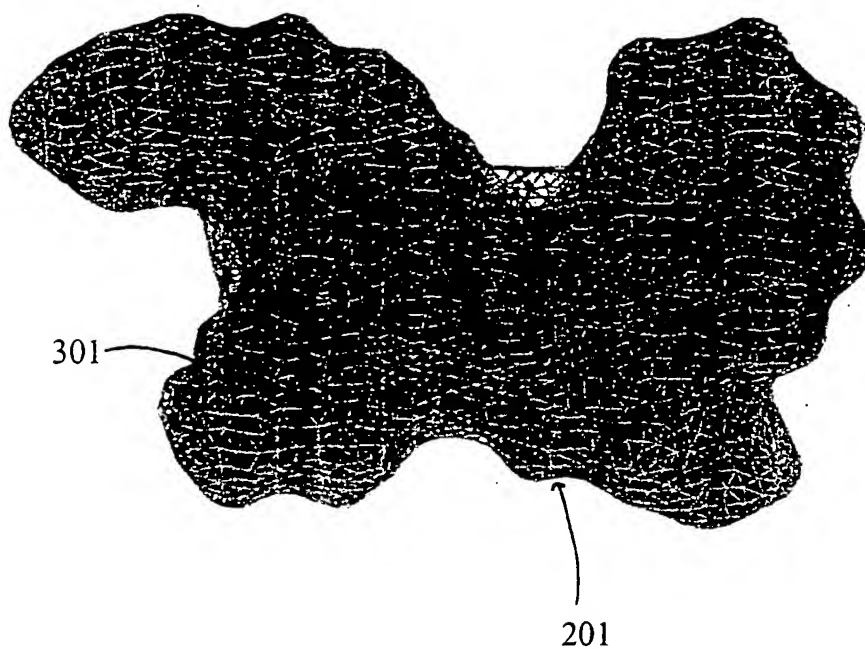


FIG. 4B

Computer Aided Ligand-Based and Receptor-Based
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REPLACEMENT SHEET

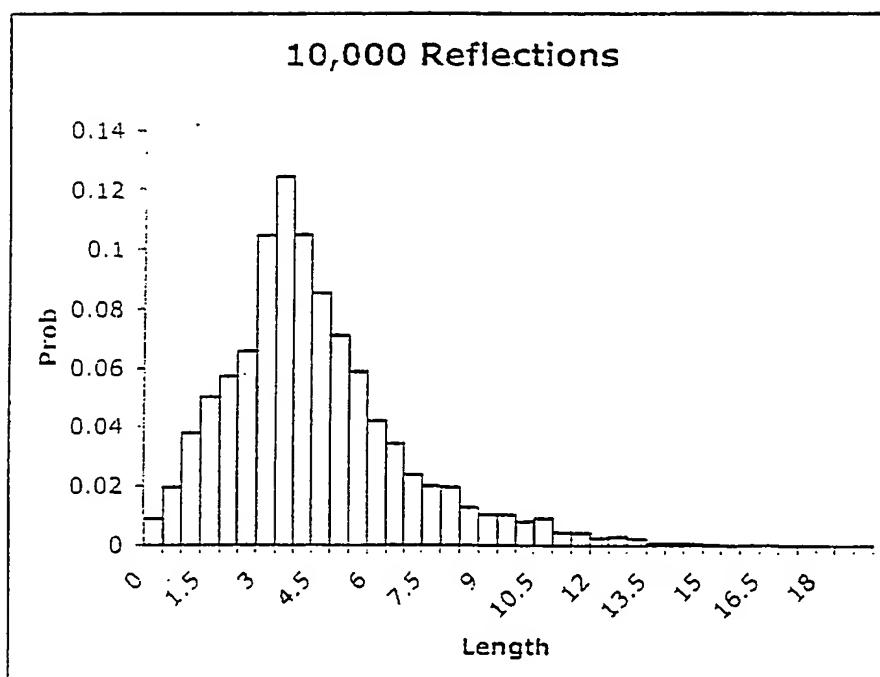


FIG. 5A

REPLACEMENT SHEET

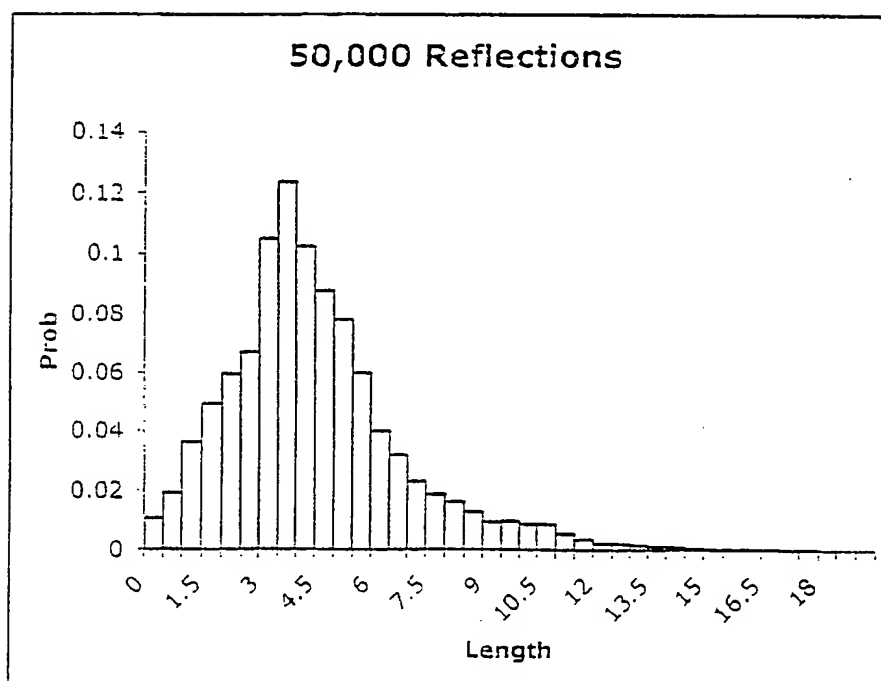


FIG. 5B

REPLACEMENT SHEET

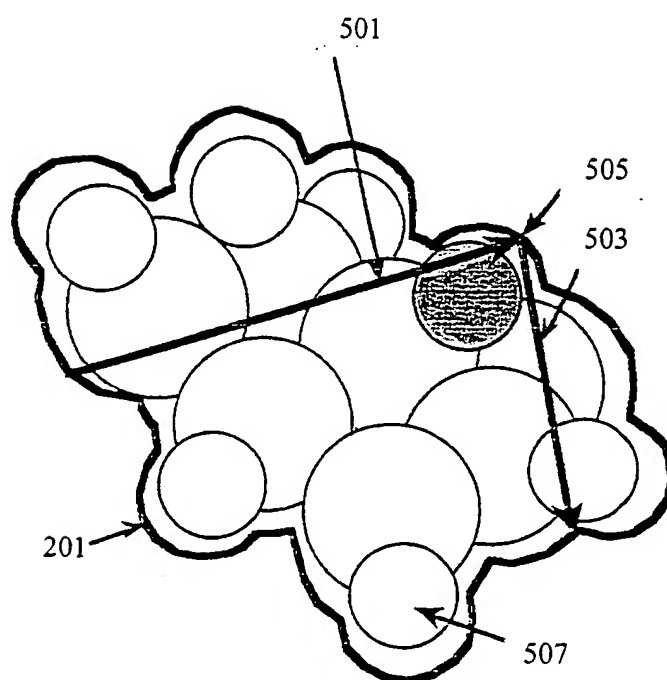


FIG. 6

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REPLACEMENT SHEET

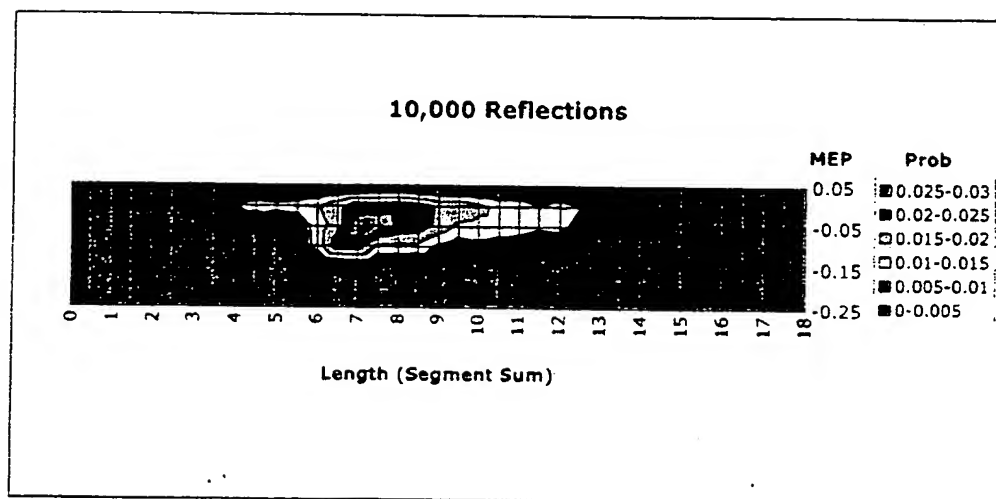


FIG. 7A

Computer Aided Ligand-Based and Receptor-Based
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REPLACEMENT SHEET

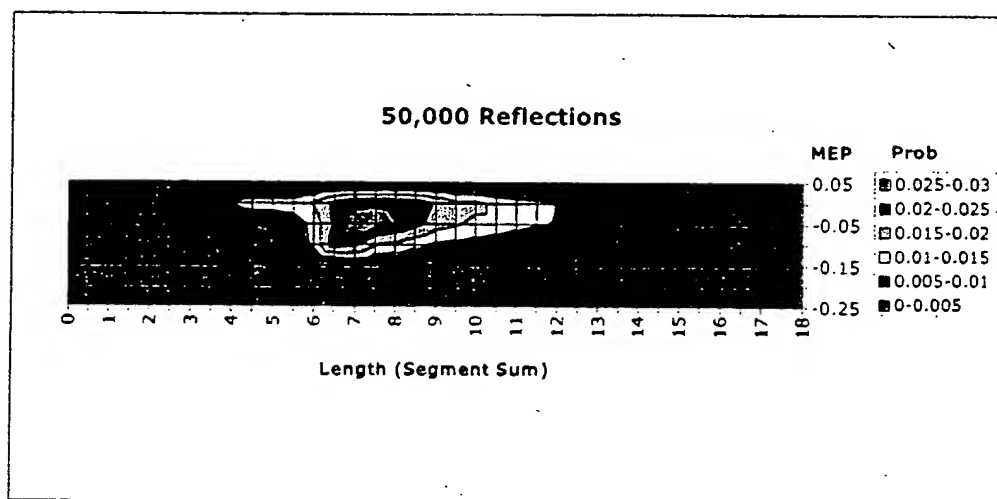


FIG. 7B

REPLACEMENT SHEET

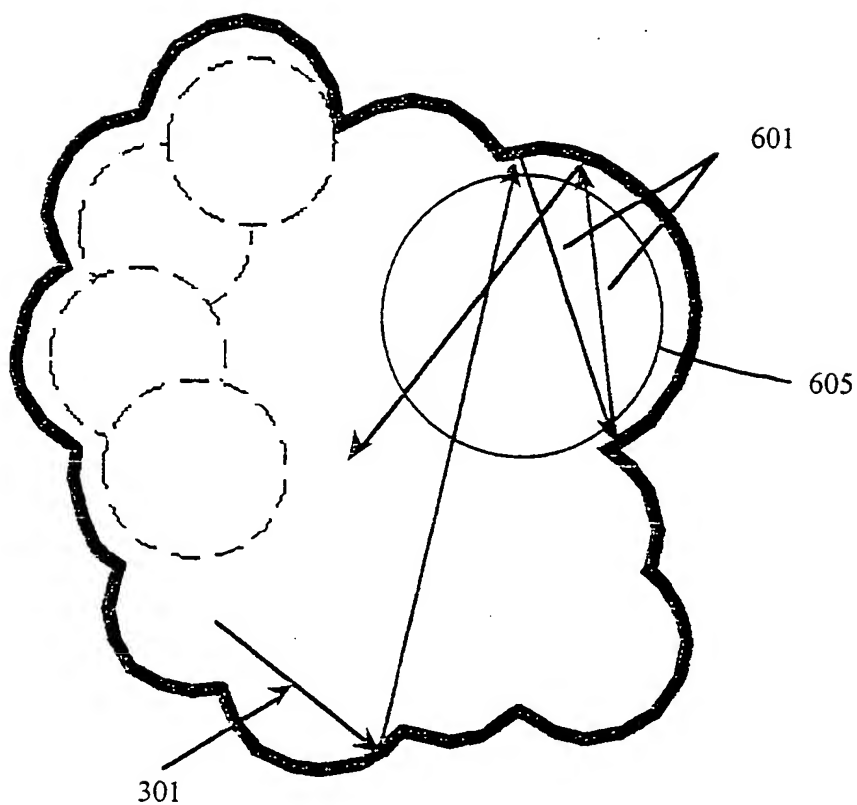


FIG. 8

REPLACEMENT SHEET

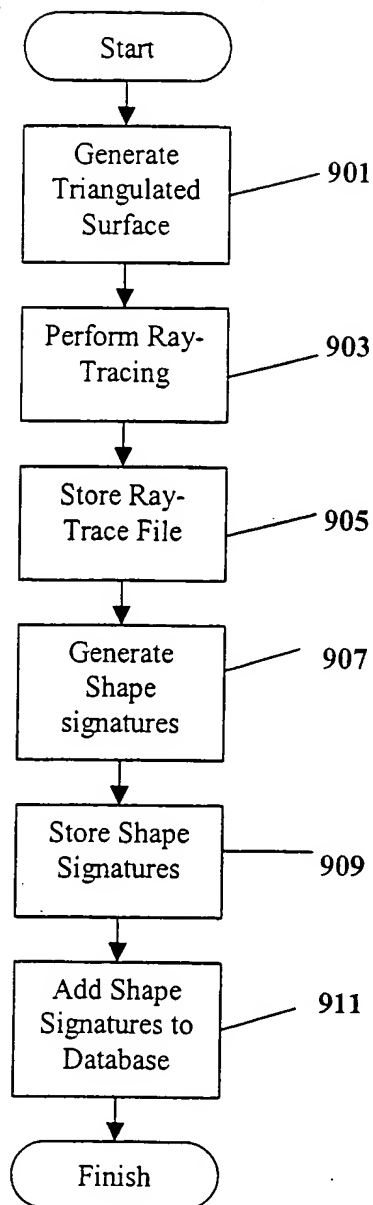


FIG. 9

REPLACEMENT SHEET

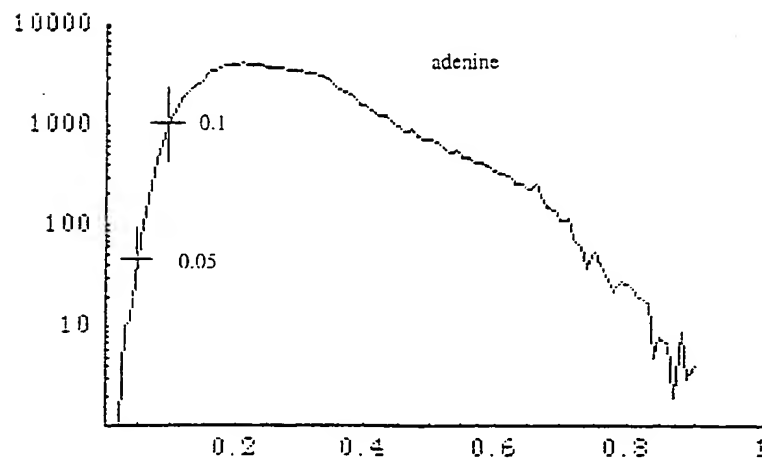
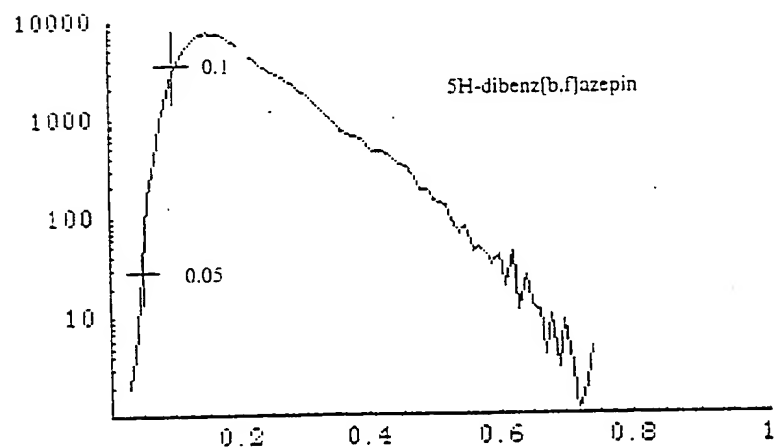
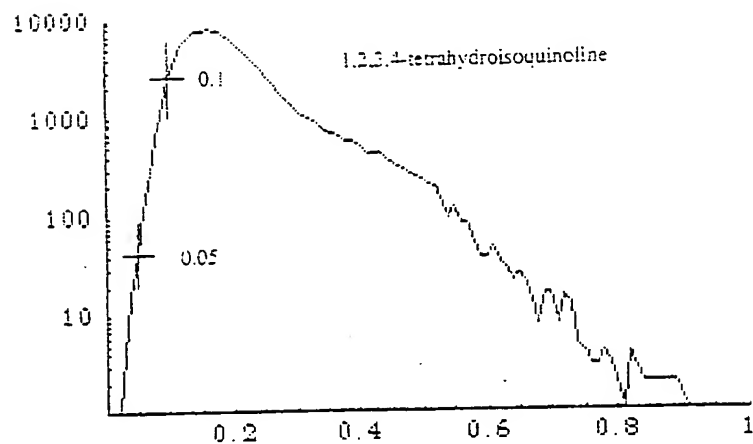


FIG. 10A

REPLACEMENT SHEET

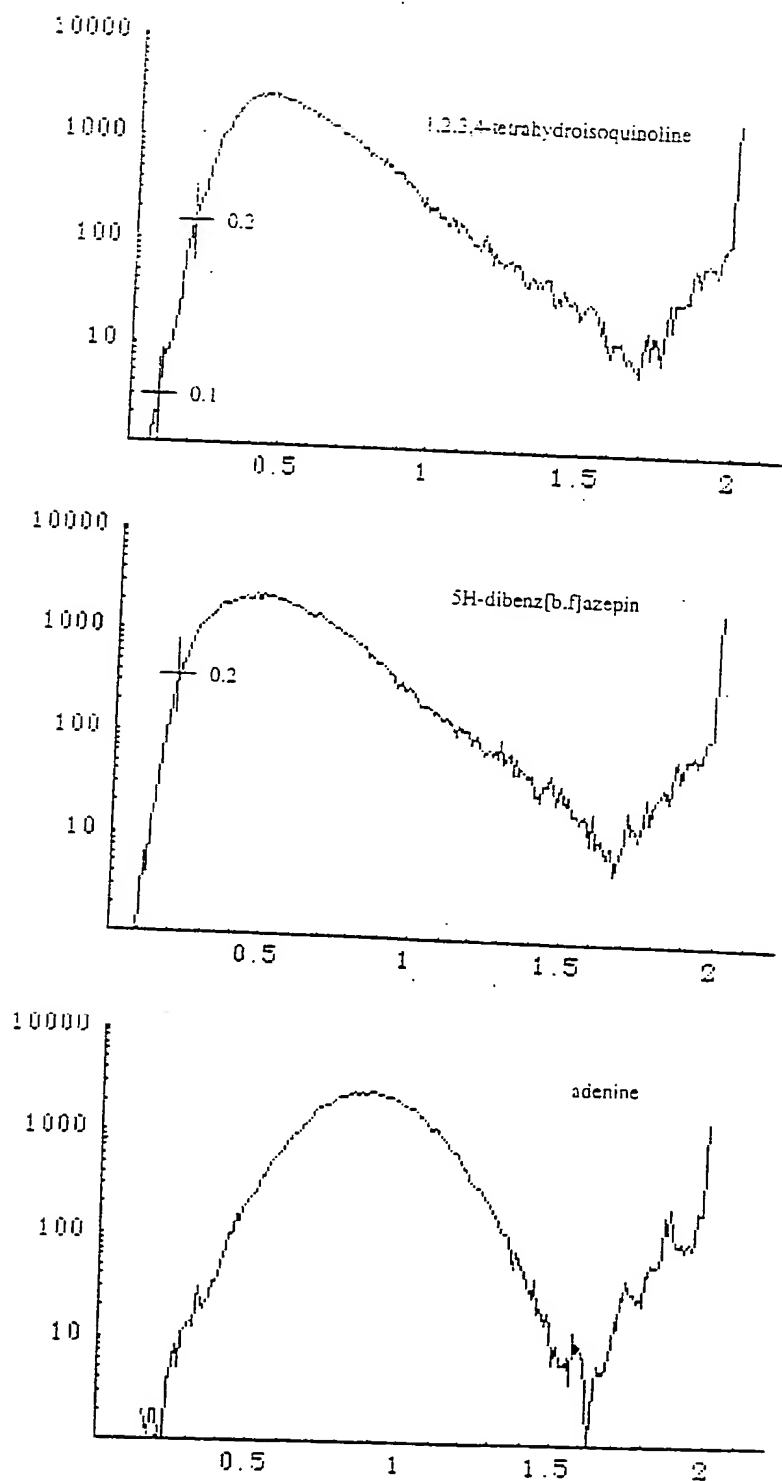


FIG. 10B

REPLACEMENT SHEET

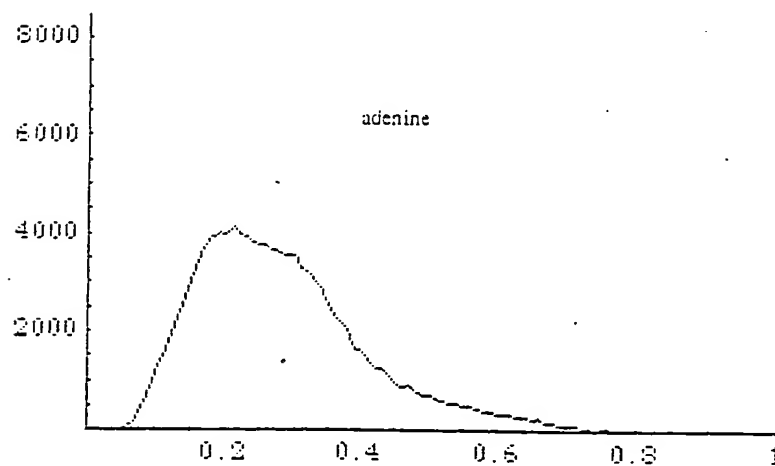
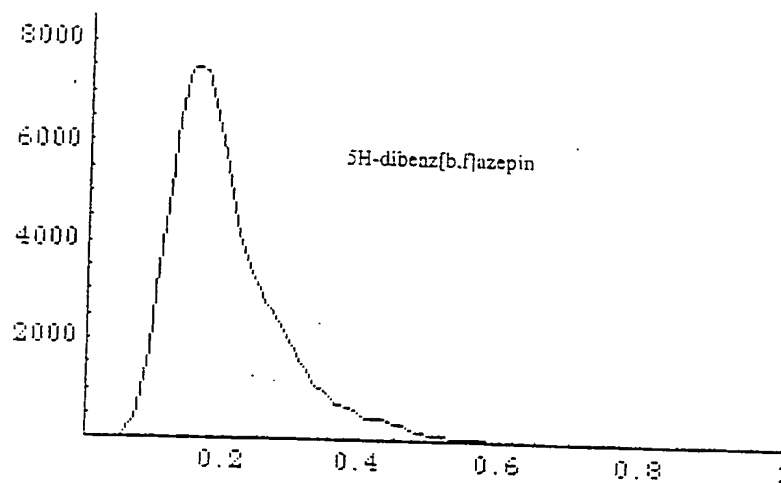
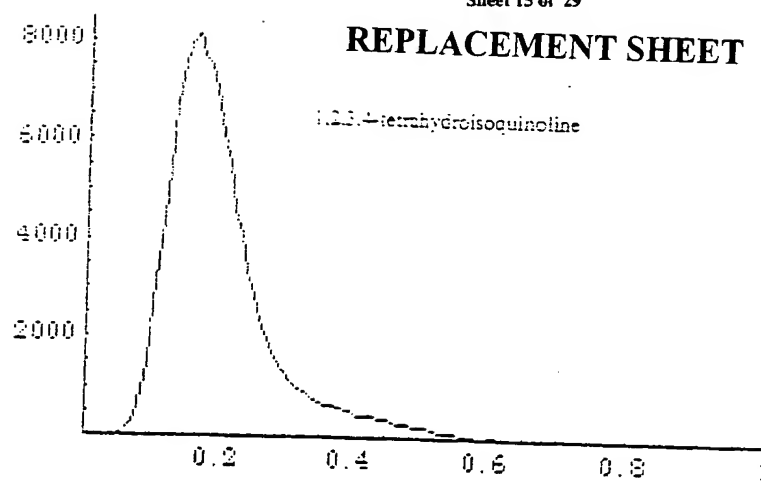


FIG. 11A

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REPLACEMENT SHEET

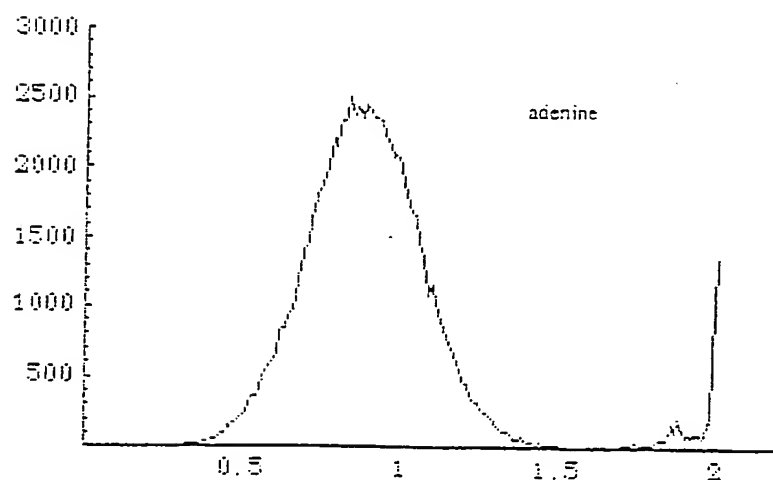
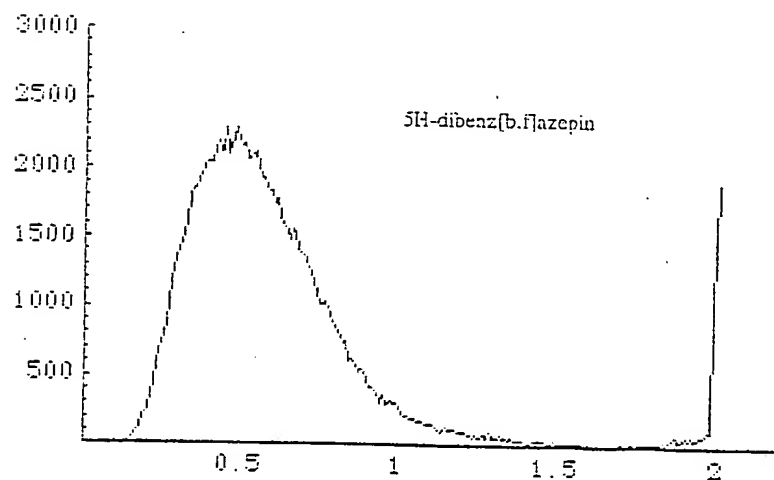
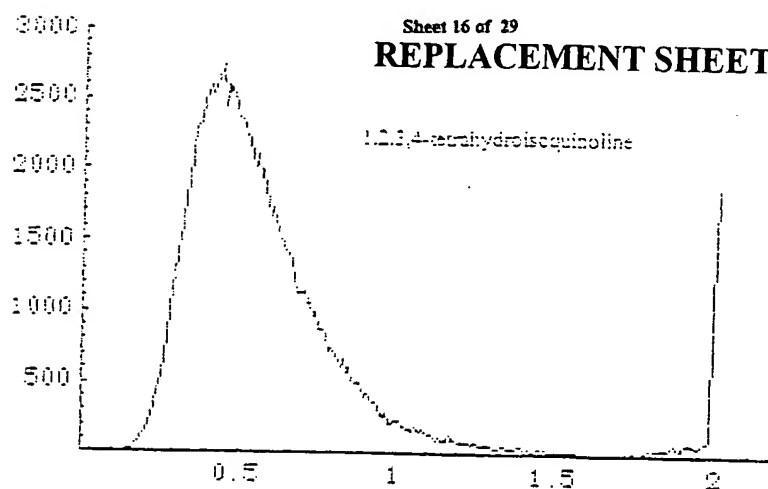


FIG. 11B

REPLACEMENT SHEET

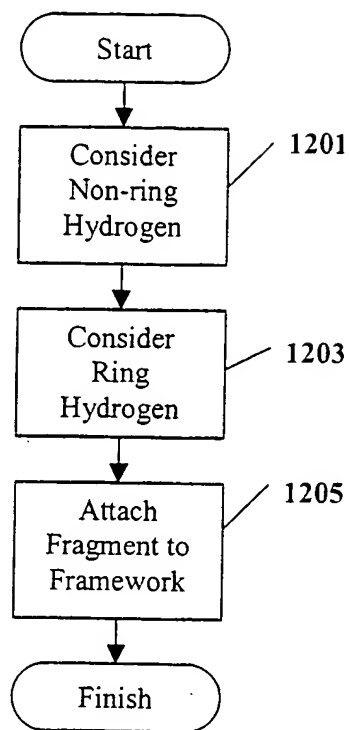


FIG. 12

Computer Aided Ligand-Based and Receptor-Based
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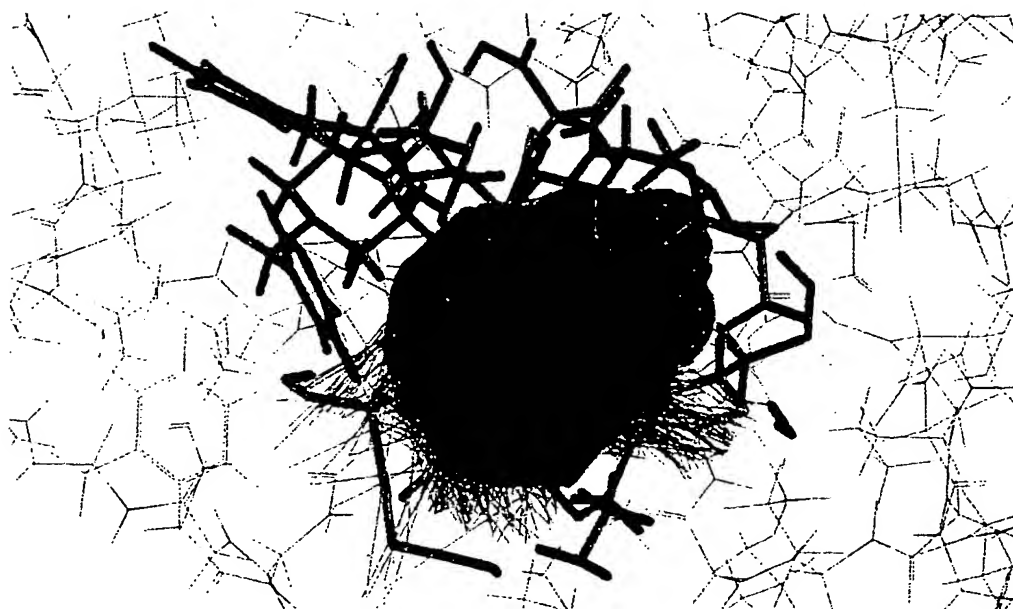


FIG. 13A

Computer Aided Ligand-Based and Receptor-Based
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REPLACEMENT SHEET



FIG. 13B

Computer Aided Ligand-Based and Receptor-Based
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REPLACEMENT SHEET

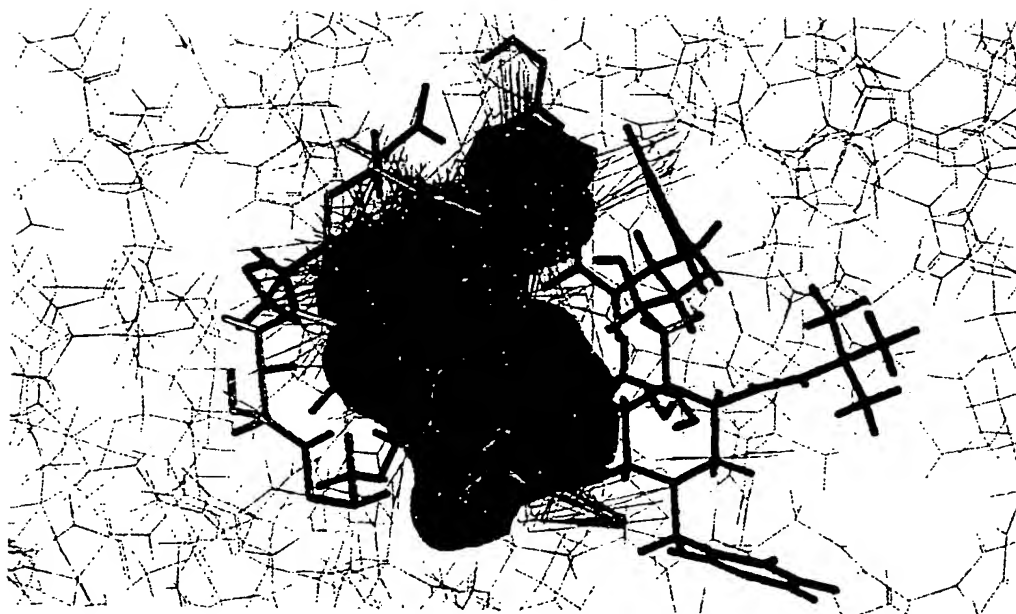


FIG. 13C

REPLACEMENT SHEET

Results for Six Query Compounds, 1-4D Shape Signature Self-Comparison of Tripos Fragment using / ₄ Metric			
QUERY	Hit Culling		No Culling
	Hit	Score	Score
1,2,3,4-tetrahydroquinoline	1,2,3,4-tetrahydroquinoline	0.0370	0.0173
	isochroman	0.0386	0.0316
	1,2,3,4-tetrahydronaphthalene	0.0490	0.0399
	chroman	0.0574	0.0475
5H-dibenz[b,f]azepin	indoline	0.0767	0.0525
	dibenzocycloheptatriene	0.0351	0.0332
	dihydrophenanthrene	0.0482	0.0384
	dioxanthene	0.0578	0.0466
1,4,6-gonatriene-3,17-dione	dibenz[b,f]thiepin	0.0695	0.0487
	5H-dibenz[b,f]-1,4-diazepine	0.0800	0.0578
	4,6-gonadiene-3,17-dione	0.0502	0.0400
	1,4-gonadien-3-one	0.0743	0.0660
α-D-glucopyranose	4-gonen-3-one	0.0984	0.0838
	1,3,5(10)-gonatriene	0.0986	0.0862
	5(10)-gonen-3-one	0.1004	0.0984
	β-D-mannopyranose	0.0417	0.0376
lysine	β-D-galactopyranose	0.0420	0.0379
	α-D-mannopyranose	0.0559	0.0391
	α-D-galactopyranose	0.0744	0.0560
	β-D-glucopyranose	0.0748	0.0766
adenine	Arginine	0.0862	0.0527
	Methionine	0.1024	0.0821
	Pantoic acid(C16)	0.1163	0.0959
	Glycerol(11)	0.1179	0.1004
benzopyrimidine	Oleate(C18)	0.1202	0.1006
	guanine	0.0626	0.0388
	7H-purine	0.0712	0.0701
	cytosine	0.0840	0.0743
	uracil	0.0854	0.0747
	benzoxazole	0.0860	0.0775

FIG. 14A

REPLACEMENT SHEET

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FIG.
14B

RESULTS FOR SIX QUERY COMPOUNDS, 1-D SHAPE SIGNATURE SELF-COMPARISON OF TRIPPOS FRAGMENT DATABASE USING L ₁ METRIC					
QUERIES					
HT #1	#2	#3	#4	#5	
1,2,3,4-tetrahydro-quinoline	isochroman	1,2,3,4-tetrahydro-naphthalene	chroman	indoline	
5H-dibenz[b,f]-azepin	dihydrophenanthrene	thioxanthene	dibenz[b,f]thiepin	5H-dibenz[b,f]-1,4-diazepine	
1,4,6-gonatriene-3,1,7-dione					
α -D-glucopyranose	β -D-mannopyranose	β -D-galactopyranose	α -D-mannopyranose	α -D-galactopyranose	β -D-glucopyranose
Lysine	Arginine	Methionine	Palmitoleate	glycerol	Oleate
adenine	guanine	7H-purine	cytosine	uracil	benzopyrimidine

REPLACEMENT SHEET

Results for Six Query Compounds, 2D-MLP Shape Signature Self-Comparison of Tripos Fragment Database using
L₁ Metric

QUERY	Colling		No Colling	
	Hit	Score	Hit	Score
1,2,3,4-tetrahydroisoquinoline	1,2,3,4-tetrahydroquinoline 1,2,3,4-tetrahydronaphthalene indoline acenaphthene indan	0.0847 0.1496 0.1732 0.1908 0.2161	1,2,3,4-tetrahydroquinoline 1,2,3,4-tetrahydronaphthalene indoline indan acenaphthene	0.0762 0.1307 0.1320 0.1554 0.1804
5H-dibenz[b,f]azepin	dibenzocycloheptatriene acridan 5H-dibenz[b,f]-1,4-diazepine 1,2,3,4-tetrahydroisoquinoline 1,2,3,4-tetrahydroquinoline	0.1116 0.2089 0.2109 0.2268 0.2292	dibenzocycloheptatriene acridan 5H-dibenz[b,f]-1,4-diazepine phenanthridine dihydrophenanthrene	0.1031 0.1538 0.1672 0.1762 0.1802
1,4,6-gonatriene-3,17-dione	4,6-gonadiene-3,17-dione 5a-gonane-3,17-dione 1,4-gonadien-3-one 5a-gonan-3-one 5a-gonan-17-one	0.0888 0.1383 0.2028 0.2031 0.2241	4,6-gonadiene-3,17-dione 5a-gonane-3,17-dione 1,4-gonadien-3-one 4-gonen-3-one 5a-gonan-3-one	0.0852 0.1383 0.2097 0.2122 0.2221
2-deoxy-β-D-ribofuranose	β-D-ribofuranose β-D-glucopyranose α-D-fructofuranose α-D-galactopyranose α-D-mannopyranose	0.2292 0.2368 0.2480 0.2616 0.2696	β-D-glucopyranose α-D-fructofuranose α-D-mannopyranose β-D-ribofuranose α-D-glucopyranose	0.2223 0.2317 0.2437 0.2445 0.2575
Lysine	Arginine ethanolamine choline D-Threose D-Xylose	0.6615 0.7882 1.2682 1.5332 1.5667	Arginine ethanolamine choline D-Threose D-Xylose	0.6617 0.7621 1.2442 1.4601 1.4912
adenine	pteridine benzothiazole guanine 7H-purine indene	0.4025 0.4321 0.4394 0.4427 0.4614	benzothiazole pteridine thiazole 7H-purine guanine	0.3493 0.3816 0.3981 0.4254 0.4265

FIG. 15

REPLACEMENT SHEET

Results for Six Query Compounds, 1D Shape Signature Comparison of
Tripos Fragment Database against the NCI Database using L_r and R_r Metrics

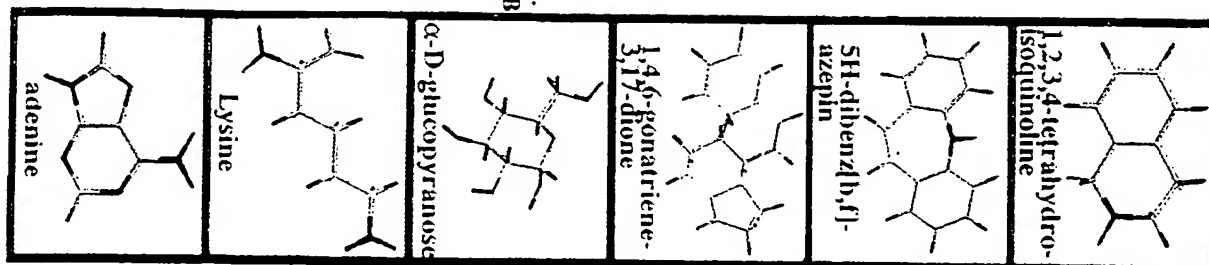
QUERY	L_r Metric		R_r Metric	
	Hit	Score	Hit	Score
1,2,3,4-tetrahydroisoquinoline	91-21-4	0.0291	91-21-4	0.1153
	10500-57-9	0.0336	10500-57-9	0.1409
	529-35-1	0.0348	578-54-1	0.1428
5H-dibenz[b,f]azepin	578-54-1	0.0380	493-05-0	0.1534
	24206-39-1	0.0397	529-35-1	0.1743
	833-48-7	0.0324	833-48-7	0.1404
1,4,6-gonatriene-3,17-dione	1211-06-9	0.0360	1211-06-9	0.1673
	10354-00-4	0.0415	10354-00-4	0.1789
	82-53-1	0.0441	42263-75-2	0.2142
α -D-glucopyranose	6279-16-9	0.0488	51087-02-6	0.2300
	24640-00-4	0.0450	6126-58-5	0.2289
	10448-96-1	0.0556	24640-00-4	0.2561
Lysine	438-67-5	0.0570	6968-06-5	0.2672
	5976-74-9	0.0576	20919-82-8	0.2908
	6126-58-5	0.0584	3601-97-6	0.2963
adenine	488-66-4	0.0546	74561-03-8	0.2223
	23559-36-6	0.0548	488-66-4	0.2548
	74561-03-8	0.0553	488-64-2	0.2548
adenine	16503-91-2	0.0607	6623-68-3	0.2548
	39392-65-9	0.0655	2037-48-1	0.2549
	5329-79-3	0.0478	37149-01-2	0.1874
adenine	110-97-4	0.0486	6963-39-9	0.1882
	5343-35-1	0.0552	110-97-4	0.2107
	37149-01-2	0.0555	6281-43-2	0.2201
adenine	7356-00-5	0.0563	104-50-7	0.2224
	10325-61-8	0.0271	10325-61-8	0.0944
	54346-27-9	0.0304	54346-27-9	0.0988
adenine	73-24-5	0.0310	5426-35-7	0.1178
	1123-54-2	0.0343	73-24-5	0.1178
	2227-98-7	0.0353	19165-47-0	0.1178

FIG. 16A

REPLACEMENT SHEET

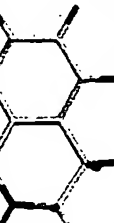
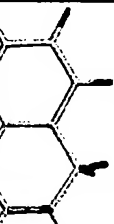
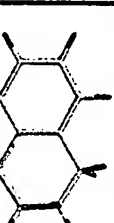
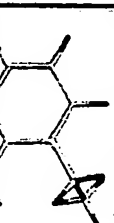

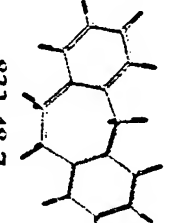
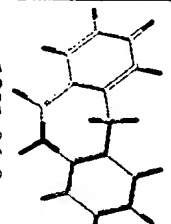
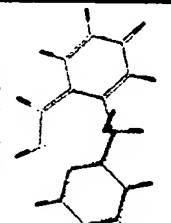
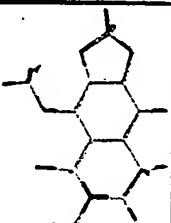
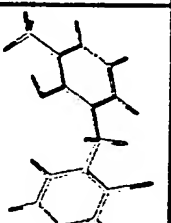
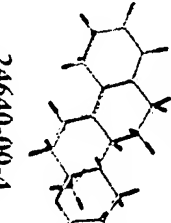
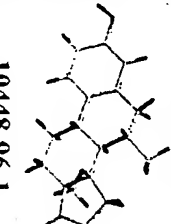
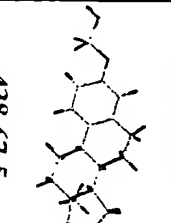
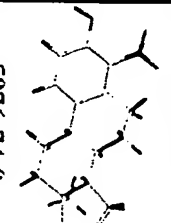
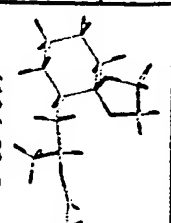


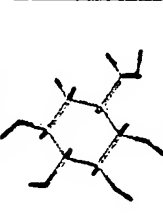
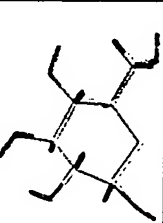
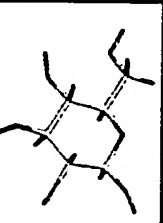
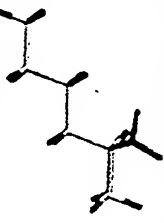
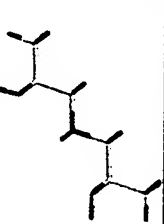
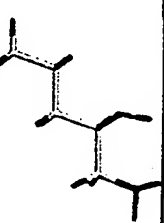
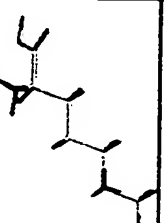
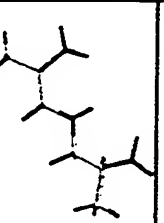
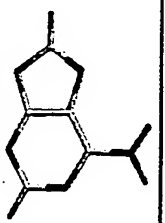
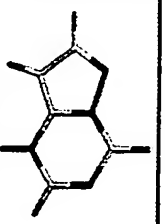
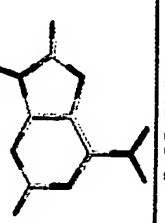
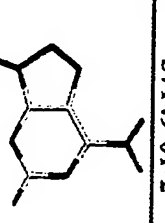
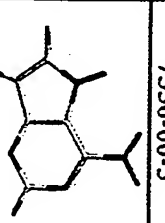
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FIG.
16B



QUERIES

Results for Six Query Compounds, 1-D Shape Signature Comparison of Tripos Fragment Database vs. NCI

HIT #1	#2	#3	#4	#5
 91-21-4	 10500-57-9	 529-35-1	 578-54-1	 24206-39-1
 833-48-7	 1211-06-9	 10354-00-4	 82-53-1	 6279-16-9
 24640-00-4	 10448-96-1	 438-67-5	 5976-74-9	 6126-58-5
 488-66-4	 23559-36-6	 74561-03-8	 16505-91-2	 39382-65-9
 5329-79-3	 110-97-4	 5343-35-1	 37149-01-2	 7356-00-5
 10325-61-8	 54346-27-9	 73-24-5	 1123-54-2	 2227-98-7

REPLACEMENT SHEET

Results for Six Query Compounds, 2D-MED Shape Signature Comparison of Tripos Fragment Database against the NCI Database using L_T and R_T Metrics					
QUERY	L_T Metric		R_T Metric		Score
	Hit	Score	Hit	Score	
1,2,3,4-tetrahydroisoquinoline	91-21-4	0.0701	91-21-4	0.5232	
	635-46-1	0.0816	635-46-1	0.6553	
	1484-19-1	0.0940	1484-19-1	0.6977	
511-dihenzylflazepin	1780-19-4	0.0983	5344-99-0	0.7295	
	5344-99-0	0.1011	1780-19-4	0.8070	
	30646-39-0	0.0947	30646-39-0	0.8078	
1,4,6-gonatriene-3,17-dione	16886-10-5	0.1079	3377-71-7	0.9075	
	32446-13-2	0.1089	16886-10-5	0.9104	
	3377-71-7	0.1126	32446-13-2	0.9166	
α -D-glucopyranose	833-48-7	0.1167	833-48-7	0.9411	
	56763-86-1	0.1524	20056-05-7	1.3418	
	734-32-7	0.1645	56763-86-1	1.3451	
Lysine	93998-31-3	0.1682	74924-17-7	1.4169	
	20056-05-7	0.1693	734-32-7	1.4949	
	74924-17-7	0.1702	71837-43-9	1.5131	
adenine	52019-14-4	0.1815	52019-14-4	1.4065	
	49871-87-6	0.1833	58691-27-3	1.4270	
	58691-27-3	0.1912	49871-87-6	1.4514	
adenine	7404-25-3	0.2015	2280-44-6	1.5418	
	14215-77-1	0.2018	14215-77-1	1.5520	
	42021-74-9	0.5473	85385-47-3	4.1381	
adenine	58048-33-2	0.5549	58048-33-2	4.2359	
	58048-35-4	0.5684	42021-74-9	4.2441	
	37082-52-3	0.5719	78582-26-0	4.3301	
adenine	78582-26-0	0.5721	62194-88-1	4.3458	
	73-24-5	0.0683	73-24-5	0.5048	
	28128-33-8	0.1537	28128-33-8	1.0824	
adenine	7390-62-7	0.1581	7390-62-7	1.2106	
	2846-89-1	0.1744	2846-89-1	1.2491	
	3647-48-1	0.1820	1904-98-9	1.2947	

FIG. 17A

REPLACEMENT SHEET

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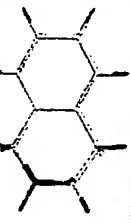


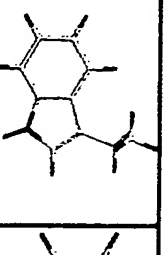
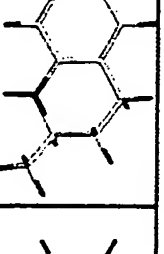
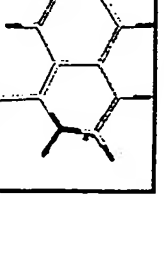
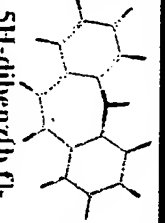
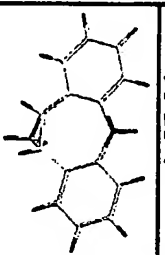
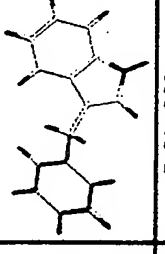
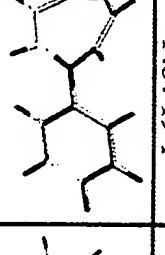
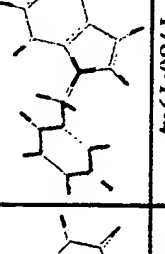
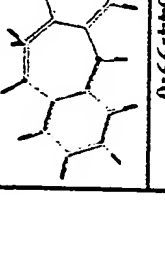
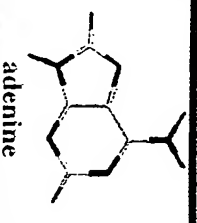
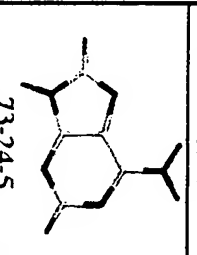
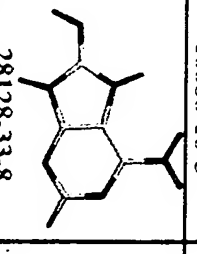
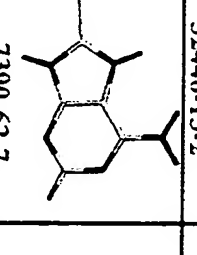
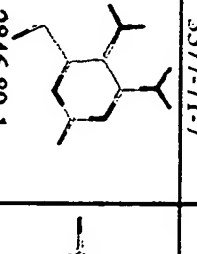
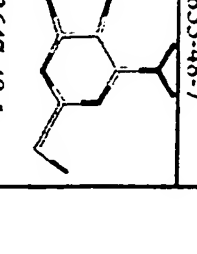
QUERIES		Results for Three Query Compounds, 2D-MEP Shape Signature, Tripos Fragment Database vs. NCI				
		HIT #1	#2	#3	#4	#5
	1,2,3,4-tetrahydro-isoquinoline					
	SH-dibenz[b,f]-azepin					
	adenine					

FIG. 17B

REPLACEMENT SHEET

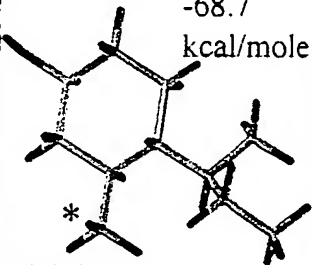
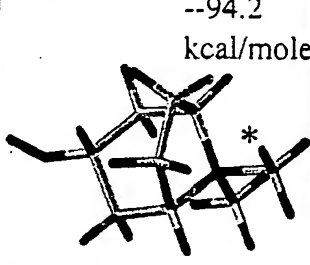
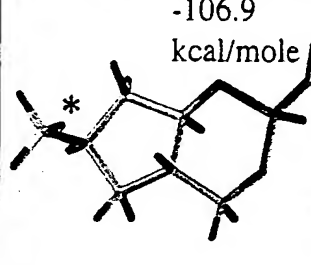
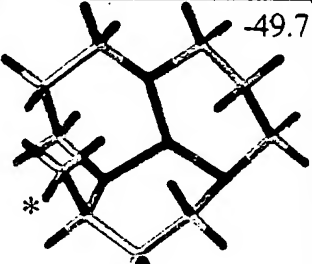
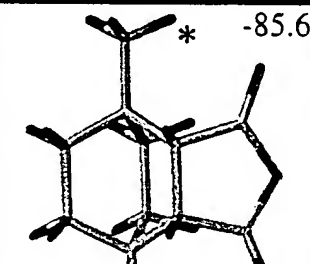
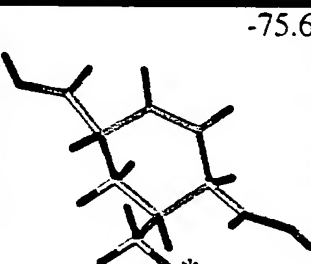
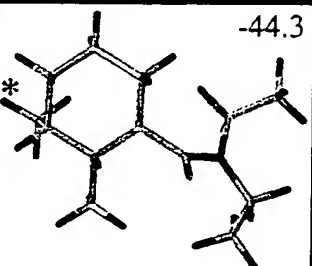
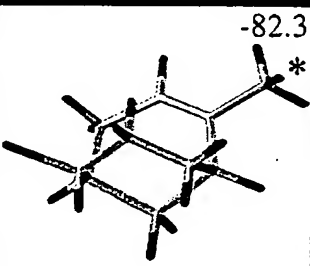
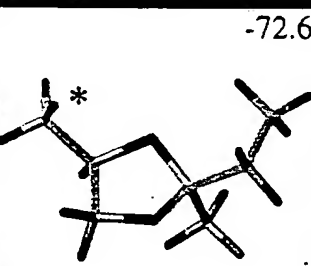
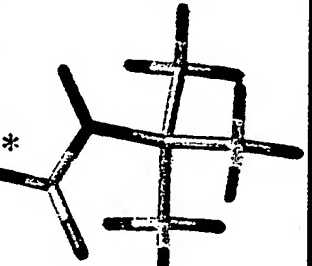
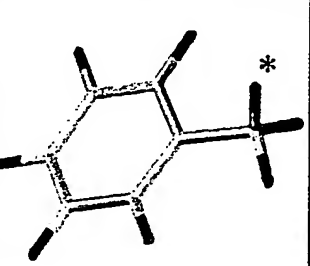
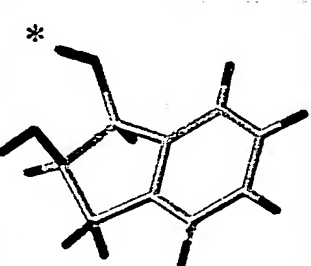
	R2	R3	R4
#1	 <p>-68.7 kcal/mole</p> <p>5396-90-7</p>	 <p>--94.2 kcal/mole</p> <p>18650-61-8</p>	 <p>-106.9 kcal/mole</p> <p>73581-87-0</p>
#2	 <p>-49.7</p> <p>62051-24-5</p>	 <p>-85.6</p> <p>26843-47-0</p>	 <p>-75.6</p> <p>19618-93-0</p>
#3	 <p>-44.3</p> <p>54243-68-4</p>	 <p>-82.3</p> <p>15298-66-5</p>	 <p>-72.6</p> <p>2916-28-1</p>
Indinavir			

FIG. 18

REPLACEMENT SHEET

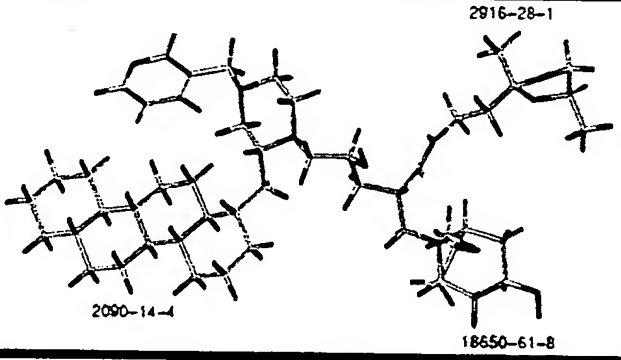
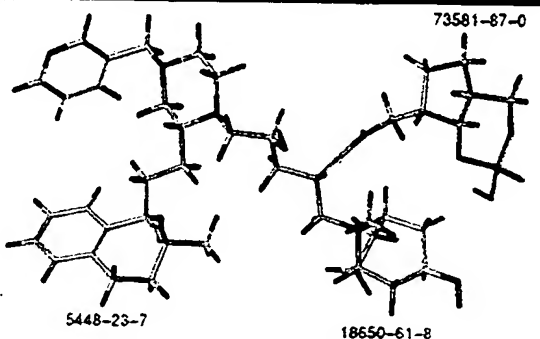
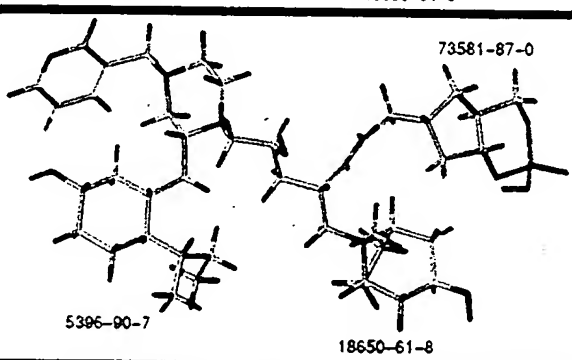
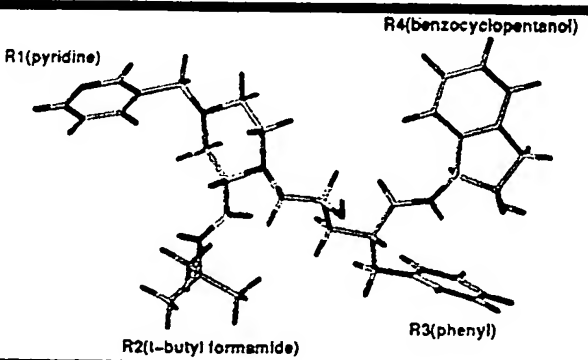
Rank	Energy(kcal/mol)	Structure
#1	-117.3	 <p>2916-28-1 2090-14-4 18650-61-8</p>
#2	-117.0	 <p>73581-87-0 5448-23-7 18650-61-8</p>
#4	-115.2	 <p>73581-87-0 5396-90-7 18650-61-8</p>
Indinavir	-97.2	 <p>R1(pyridine) R2(<i>l</i>-butyl formamide) R3(phenyl) R4(benzocyclopentanol)</p>

FIG. 19

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